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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/869,565	10/17/2001	Thomas J. Gardella	0609.4730000	4604

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EXAMINER	
KAPUST, RACHEL B	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 05/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/869,565	GARDELLA ET AL.	
	Examiner	Art Unit	
	Rachel B. Kapust	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 October 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election **without** traverse of Group IV, directed to a method of screening for agonists or antagonists of parathyroid hormone (PTH) receptor activity, is acknowledged. Claims 1-18 have been canceled. Claims 20-26 have been added. Although the application number listed at the top of the claims is 09/672,020, the Examiner is assuming that they are meant to be the claims for 09/869565. Claims 19-26 are pending and under consideration.

Specification

The disclosure is objected to because of the following informalities: Figure 1 contains amino acid or nucleic acid sequences. Applicants are directed to 37 C.F.R. § 1.821(d)

> (d) Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

In order to comply with 37 C.F.R. 1.821, appropriate correction is required. The objection can be obviated by amending the brief description of Figure 1 on page 4 to include the proper sequence identifier for the nucleic acid and amino acid sequences listed in Figure 1.

The use of the trademark SEP-PAK (p. 25) has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 19-26 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: determining whether a test compound is an agonist or an antagonist. The claims are drawn to methods of screening for agonists or antagonists of PTH receptor activity, however the final step of the methods is measuring the biological response of cells. Without knowing whether a particular biological response is increased or decreased, one skilled in the art would not know whether a compound is an agonist or an antagonist to a PTH receptor.

Claims 19, 20, and 22-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 19, 20, and 22-26 are drawn to methods of measuring a "biological response" of cells. One skilled in the art would not know what the metes and bounds of a "biological response" are. The term is not defined by the claim, and although Applicants teach on p. 28 that a biological/cellular response is intended to be "qualitatively or quantitatively measuring a cellular response to a candidate compound and/or PTH or PTHrP", one skilled in the art would not be reasonably apprised of the scope of the invention. The only biological response taught by Applicants is measuring cAMP accumulation. It is unclear what other biological responses would be appropriate for measuring in order to determine whether a compound is an agonist or antagonist of a PTH receptor.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 20-26 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The invention appears to employ novel biological materials, specifically the cDNA of the clone deposited as ATCC Deposit No. PGA-1136. Since the biological materials are essential to the claimed invention, they must be obtainable by a repeatable method set forth in the specification or otherwise readily available to the public. If the biological materials are not so obtainable or available, the requirements of 35 U.S.C. § 112 may be satisfied by a deposit of the biological materials. It is noted that Applicants appear to have deposited the biological materials (p. 7 of the specification), but there is no indication in the specification as to the date of deposit or to public availability. If the deposit is made under the Budapest Treaty, then an affidavit or declaration by Applicants, or a statement by an attorney of record over his or her signature and registration number, stating that the specific biological materials have been deposited under the Budapest Treaty and that the biological materials will be irrevocably and without restriction or condition released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein. If the deposit has *not* been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 C.F.R. §§ 1.801-1.809, Applicants may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that:

(a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained in a public depository for a period of 30 years of 5 years after the last request or for the effective life of the patent, whichever is longer;

(d) a test of viability of the biological material at the time of deposit will be made (see 37 C.F.R. § 1.807); and

(e) the deposit will be replaced if it should ever become unviable.

Applicant's attention is directed to MPEP § 2400 in general, and specifically to § 2411.05, as well as to 37 C.F.R. § 1.809(d), wherein it is set forth that "the specification shall contain the accession number for the deposit, the date of the deposit, the name and address of the depository, and a description of the deposited material sufficient to specifically identify it and to permit examination." The specification should be amended to include this information, however Applicants are cautioned to avoid the entry of new matter into the specification by adding any other information.

Claims 19, 20, and 22-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of screening for agonists or antagonists of a polypeptide by measuring the amount of cAMP accumulation, does not reasonably provide enablement for a method of screening for agonists or antagonists of a polypeptide by measuring any biological response. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention; 2) state of the prior art; 3) relative skill of those in the art; 4) level of predictability in the art; 5) existence of working examples; 6) breadth of claims; 7) amount of direction or guidance by the inventor; and 8) quantity of experimentation needed to make and/or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Applicants have provided little or no guidance to enable one of skill in the art to determine, without undue experimentation, what changes in a biological responses are indicative of a compound being an agonist or antagonist of a PTH receptor. Applicants teach that measuring the accumulation of cAMP is one means of determining whether a compound is an agonist or antagonist (p. 25), however that is only one biological response out of an infinite number that can be measured. One of skill in the art would not know whether measuring any biological response such as a change in pH, change in the flow of ions, etc. would be a sufficient indication as to whether a compound is an antagonist or agonist of a PTH receptor. Applicants do not provide adequate guidance but merely provide an invitation to the artisan to use the current invention as a starting point for further experimentation.

Due to the large quantity of experimentation necessary to determine what biological responses would be indicative of a change in the activity of a PTH receptor, the lack of direction/guidance presented in the specification, the absence of working examples directed to biological responses other than cAMP accumulation, the complex nature of the invention, and the breadth of the claims, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

Claims 20-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of screening for agonists or antagonists of a polypeptide comprising the amino acid sequence of SEQ ID NO: 2, does not reasonably provide enablement for a method of screening for agonists or antagonists of polypeptides that are 95% identical to SEQ ID NO: 2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 20-24 are drawn to methods of screening for agonists or antagonists of PTH receptor activity by contacting test compounds to cells expressing polypeptides that are at least 95% identical to SEQ ID NO: 2. The claims do not contain any functional limitations for the polypeptide variants, and the polypeptides could have structures and functions that are very different from that of SEQ ID NO: 2. Applicants have provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein that are tolerant to change and the nature and extent of changes that can be made in these positions. Although Applicants teach methods for identifying amino acids critical for protein function such as site-directed mutagenesis or alanine-scanning mutagenesis (see p. 22, line 19 through p. 23, line 6), this is not adequate guidance as to the nature of active variants that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, such as various sites or regions directly involved in binding, activity, and in providing the correct three-dimensional spatial orientation of binding and active sites. Particular regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie *et al.* (1990), *Science* 247: 1306-1310, especially p. 1306, column 2, paragraph 2; Wells (1990), *Biochemistry* 29: 8509-8517; Ngo *et al.* (1994), The

Protein Folding Problem and Tertiary Structure Prediction, Merz *et al.*, eds., Birkhauser, Boston, pp. 14-16).

Due to the large quantity of experimentation necessary to generate the large number of variants recited in the claims and screen the same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

In addition, claims 20-24 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims are drawn to a genus, *i.e.* a method of screening for agonists or antagonists of proteins of at least 95% identity to SEQ ID NO: 2. Applicants have disclosed one species, a method of screening for agonists or antagonists of the polypeptide of SEQ ID NO: 2, but have not disclosed sufficient species for the broad genus which encompasses any protein at least 95% identical to SEQ ID NO: 2.

The instant disclosure of a single species of polypeptide does not adequately describe the scope of the claimed genus, which encompasses methods of screening hundreds of different polypeptides with varying structures and functions. A description of a genus of polypeptides may be achieved by means of a recitation of a representative number of polypeptides, defined by amino acid sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, said features constituting a substantial portion of the genus. The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the claimed genus of polypeptides. There is no description of the conserved regions which are critical to the structure and function of the genus claimed. Thus, no identifying characteristics or properties of the instant polypeptides are provided such that one

of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed.

Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, the disclosure of SEQ ID NO: 2 is insufficient to describe the genus. Therefore, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 19-24 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,494,806. Claim 19 is drawn to a method of screening for agonists or antagonists of PTH receptors. Claims 20-24 are drawn to contacting cells expressing polypeptides having amino acid sequences at least 95% identical to SEQ ID NO: 2 with test compounds. The '806 patent teaches methods for screening for agonists or antagonists of PTH receptors by contacting cells expressing a PTH receptor with a test compound (see column 22, line 46 through column 23, line 22). cAMP accumulation, intracellular calcium, and/or inosital phosphate assays may be used for measuring changes in PTH receptor activity. The '806 patent teaches the nucleic acid sequence and amino acid sequence of rat PTH receptor which is 96.1% identical to SEQ ID NO: 2 (see attached alignment). Thus, claims 19-24 are anticipated by the '806 patent.

Claim 19 is rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,495,662. Claim 19 is drawn to a method of screening for agonists or antagonists of PTH receptor activity by contacting a test compound to cells expressing a PTH receptor and measuring the biological response of the cells. The '662 patent teaches a method of screening for agonists and antagonists of the PTH-1 receptor by incubating cells expressing the PTH-1 receptor with a test compound and then measuring cAMP accumulation (see column 23, lines 29-41). Antagonists inhibit cAMP accumulation and agonists stimulate cAMP accumation. Thus, claim 19 is anticipated by the '662 patent.

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Conclusion

NO CLAIMS ARE ALLOWED.

The following articles, patents, and published patent applications were found by the Examiner during the art search while not relied upon are considered pertinent to the instant application:

WO 00/47729 A1 (Pirie-Shepherd *et al.*)

Chorev *et al.* (1991) *Biochemistry* 30(24): 5968-5974

Goud *et al.* (1991) *J Bone Miner Res* 6(8): 781-789

Horiuchi *et al.* (1987) *Am J Physiol* 253: E187-192

Lee *et al.* (1995) *Mol Endocrinol* 9(10): 1269-1278

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rachel B. Kapust whose telephone number is (571) 272-0886. The examiner can normally be reached on Mon-Fri 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (571) 272-0887. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

RBK
5/14/04

JANET ANDRES
PATENT EXAMINER